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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,245	07/22/2003	Shuichi Mizuno	3831.08	9296

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,245	MIZUNO ET AL.	
	Examiner	Art Unit	
	David M. Naff	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/8/07 has been entered.

An amendment of 8/8/07 canceled claims 43-62 (1-42 previously canceled), and added new claims 63-82.

Claims examined on the merits are 63-82, which are all claims in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support is not readily apparent in the specification for isolating chondrocytes from joint cartilage in step a) of claims 63 and 78, the alternatives of a collagen containing solution, gel and thermo-reversible hydrogel in step c) of claim 63, the alternative of a collagen containing solution and thermo-reversible hydrogel in step c) of claim 78, the alternatives of a collagenous sponge, collagenous scaffold, collagenous honeycomb and collagenous honeycomb-like lattice required by lines 37-38 of claims 63 and 78, the alternatives of a collagenous sponge and collagenous honeycomb in claim 78, for "about five to about ten days" and "about ten to about fourteen days" in lines 23 and 24, respectively, of claim 78, and for a combination of types I, II and IV collagen as required in the last line of claim 79. The page and line of the specification where each of the above claim limitations is recited should be pointed out. Support is not found in the pages and lines recited on page 9 of the amendment.

Support is not found in the specification for a Markush group of alternative materials for preparing the support matrix as required by claim 64. The page and line should be pointed out where each member of the group is recited, and the members being in a combination as required by the last line of the claim. Support is not found in the pages and lines recited on page 9 of the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Bridging lines 5 and 6 of claims 63 and 78, "genetically activated" is uncertain as to meaning and scope. The steps subsequently required for activation do not appear to be steps that would normally be considered to be "genetically".

Claims 63 and 78 are confusing by further defining conditions of steps a) and d) near the end of the claims in lines 31-39 separate from where the steps initially required. All conditions of steps a) and d) should be set forth where the steps are initially required.

Claims 63 and 78 are unclear in lines 25 and 26 as to material in the activation step the perfusion medium contacts when perfusion is performed.

In line 38 of claims 63 and 78, "honeycomb-like" is uncertain as to meaning and scope. Being like a honeycomb is relative and subjective.

Bridging lines 7 and 8 of claim 64, "collagen containing a synthetic polymeric fiber made of a polylactic acid" is uncertain how collagen can contain a synthetic polymeric fiber made of polylactic acid. The specification fails to describe collagen containing a fiber as claimed.

Claim 77 is confusing by requiring the matrix to be seeded with isolated and expanded chondrocytes since this is already required in claim 63. Repeating in a dependent claim conditions that are already in an independent claim makes unclear how the dependent claim further limits the independent claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 63-82 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052).

The claims are drawn to an implantable construct suitable for implanation into a cartilage lesion or defect. The construct is prepared by isolating inactive chondrocytes from joint cartilage by subjecting the cartilage to enzymatic digestion, expanding the chondrocytes in a culture medium, suspending the expanded chondrocytes in a collagen solution, gel or thermo-reversible hydrogel, seeding the suspension in a support matrix which is a collagenous sponge, scaffold, honeycomb or honeycomb-like lattice having pores 50 to 500 um in size. The seeded support is subjected to an activation step for about one week to about three months, which comprises applying to the seeded support a cyclic hydrostatic pressure from about 0.01 to 10 MPa

above atmospheric pressure at a frequency of from about 0.01 to 2 Hz for about one hour to 30 days followed by a resting period from about one day to sixty days. During activation, perfusion with a perfusion medium is performed at a flow rate from about 1 to 500 uL per minute. The formed construct comprises more than 5% of activated chondrocytes, and has a ratio of newly synthesized extracellular matrix to activated chondrocytes in the construct lower than 95:5.

Smith et al disclose repair and regeneration of cartilage by a process that involves *in vivo*, *ex vivo* or *in vitro* treatment of cartilage or cartilage cells (chondrocytes) in a support such as a scaffold or collagen matrix (col 6, lines 14-16) by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery *in situ* (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). *In* vitro treatment is performed by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, line 4). The chondrocytes can be autologous or not autologous (col 9, line 33). Articular cartilage can be regenerated and repaired (col 1, lines 41-43).

A cartilage construct produced by the process of Smith et al is the same the construct presently claimed for implantation into a cartilage lesion or defect. No difference is seen in the presently claimed process from the process of Smith et al that would result in a materially different construct. The process of Smith et al will inherently produce a construct having at least 5% activated chondrocytes, and a ratio of newly synthesized extracellular matrix to activated chondrocytes lower than 95:5.

The presently claimed invention is not disclosed in parent application 10/104,677, and the parent application cannot be relied on for a priority date earlier than the filing date the present application.

Response to Arguments

The response urges that Smith et al do not suggest a construct comprising rejuvenated chondrocytes able to produce new extracellular matrix produced by the process claimed. However, Smith et al isolate chondrocytes that are inherently mature (Example 1) since they are adult articular chondrocytes (col 16, line 65). These chondrocytes are inherently non-dividing and inactive. The present specification discloses no source of cartilage for isolating chondrocytes other than disclosed by Smith et al. Applying hydrostatic pressure at a frequency disclosed by Smith et al inherently rejuvenates the isolated chondrocytes as evidenced by Smith et al disclosing (col 11, lines 7-10) that the hydrostatic pressure increases metabolic activity and decreases expression of destructive enzymes of chondrocytes.

Claim Rejections - 35 USC § 103

Claims 63-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052) in view of Lee et al (6,306,169) and Burg (6,991,652), and if necessary in further view of Atkinson et al (6,511,958).

The invention and Smith et al are described above.

Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing in vitro in a medium containing serum (col 7, lines 20-29). Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

When incorporating chondrocytes from cartilage into a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by *in vitro* culturing in a culture medium prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting. The resultant construct will be a cartilage construct as presently claimed, and will inherently have a ratio of newly synthesized extracellular matrix to activated chondrocytes of lower than 95:5. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same or substantially the same as used in the present claims. Perfusion with a medium as claimed during treatment with hydrostatic pressure would have been obvious to provide nutrients for the cells to maintain the cells active for growth. Suspending the chondrocytes of Smith et al in a solution such as a collagen solution before seeding the cells in the matrix is suggested by Lee et al suspending cells in a solution such as collagen solution, before seeding, (col 6, line 21, and col 13, lines 11-26) that forms a second matrix component. The collagen solution would have been expected to gel and form a scaffold for the chondrocytes. The conditions of dependent claims are suggested by conditions used by the references. Lee et al suggest a sponge and Burg suggests temperature-dependent hydrogels as a matrix for seeding cells to implant. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen as in claim 70 would have been an obvious variation that would not be expected to produce a

difference in result. Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 71 is an obvious variation that would not be expected to produce a difference in result. Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

Response to Arguments

The amendment urges that Smith et al and the other references do not suggest a construct comprising rejuvenated chondrocytes able to produce new extracellular matrix produced by the process claimed. However, for reasons set forth above, this argument is unpersuasive.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David M. Naff
Primary Examiner
Art Unit 1657

DMN
10/27/07